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F A X C O V E R

Date Wednesday, November 05, 2003 **Number of pages (including cover):** 3

To Examiner Diana B. Johannsen

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MESSAGE:

Dear Examiner Johannsen,

Please find attached herewith the report issued by the Johns Hopkins Department of Psychiatry and Behavioral Sciences in January 2002, which was referenced in the amendment filed in US 09/581,500 on November 3, 2003. The report was inadvertently omitted from the envelope when the response was mailed.

Sincerely,
MaryDilys Anderson

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Discovery That Common Mood Disorders Are Inherited Together May Reveal Genetic Underpinnings

The genetic underpinnings of panic disorder and manic depressive (bipolar) illness have long eluded scientists. Now, researchers at Johns Hopkins studying the inheritance patterns of these conditions have concluded that they probably are not separate diseases at all, but different forms of a shared and complex biological condition.

"We've shown that panic attacks and panic disorder are related genetically to bipolar disorder and therefore likely share a common cause," says Dean F. MacKinnon, M.D., assistant professor of psychiatry at Hopkins and lead author of a report on the study in the current issue of the *American Journal of Psychiatry*. "We still can't say what specific gene or genes cause what, but this is a major step toward solving these problems," says MacKinnon.

The scientists' case for a common foundation emerged from examining the disease pedigrees of 203 families in which at least one family member had bipolar disorder. Interviews with family members led to the identification of symptoms characteristic of major mood disorders and other psychiatric conditions in relatives.

"We found that if one family member has both panic disorder and bipolar disorder, then the risk of panic disorder in other relatives is greatly increased," says MacKinnon. "These links reflect the genetic complexity of these disorders."

While genes may not tell the whole story of major psychiatric diseases, the persistent frequency in about 1 percent of the global human population, regardless of cultural or ethnic differences, and their tendency to run in families have always pointed to a strong genetic role.

But pinning down that role is complicated by the many variations in symptoms, even within the same family. Some, for example, have intense episodes of mania, others have mild mania, some with panic, some without.

"Gene expression is complex, and in these disorders, environmental factors and nature-nurture interactions are all certainly involved," says MacKinnon.

Further studies of families with both panic and bipolar disorder and with bipolar disorder alone should lead to other insights into both conditions, says MacKinnon. For instance, panic and bipolar disorder may be the same underlying condition marked by different degrees of intensity of such symptoms as anxiety and fear, heart palpitations, shortness of breath and dizziness. "There might be a panic flavor of bipolar disorder so that if you have bipolar disorder, you also have panic," says MacKinnon.

Alternatively, panic vulnerability may be a fairly common trait that shows itself preferentially under certain extreme forms of provocation, one of which is bipolar disorder.

"The exciting thing is that we can now begin to link up specific clinical features of these various disorders to a genetic model of complex inheritance. We see that certain family members have different varieties of disease, and now we create a model to account for this variation, and improve diagnosis and treatment," says MacKinnon.

Other authors of the study are Peter P. Zandi, M.P.H., Jennifer Cooper, M.D., James B. Potash, M.D., M.P.H., Sylvia G. Simpson, M.D., M.P.H., Elliot Gershon, M.D., John Nurnberger, M.D., Ph.D., Theodore Reich, M.D., and J. Raymond DePaulo, M.D.

The research is supported by the National Institutes of Mental Health and the NIMH Bipolar Disorder Genetics

Initiative, the Charles A. Dana Foundation Consortium on the Genetic Basis of Manic Depressive Illness, the National Alliance for Research on Schizophrenia and Depression, and the Ted and Vada Stanley Foundation.

Related Web sites:

The Johns Hopkins Department of Psychiatry and Behavioral Sciences:

<http://www.med.jhu.edu/jhhpsychiatry/master1.htm>

Depression and Related Affective Disorders Association (DRADA): <http://www.hopkinsmedicine.org/drada/>

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